(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 290 819 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **01.12.93**

(51) Int. Cl.5: **A61K 31/505**, C07D 475/02, C07D 475/04, C07D 475/06, C07D 475/08

(21) Application number: **88106141.0**

(22) Date of filing: **18.04.88**

(54) Pteridines suitable for the preparation of pharmaceutical compositions with antiamnesic activity.

(30) Priority: **14.05.87 IT 2051687**

(43) Date of publication of application:
17.11.88 Bulletin 88/46

(45) Publication of the grant of the patent:
01.12.93 Bulletin 93/48

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 164 964
US-A- 3 895 012
US-A- 4 183 934

Patent Abstracts of Japan, vol. 11, no. 167 (C-425)(2614), 28th May 1987

Journal of Organic Chemistry, vol. 36, no. 25, 1971, pp. 3925-3927, C.B. Storm

Chemical Abstracts, vol. 98, no. 9, 28th February 1983, Columbus, Ohio, US; J.H. Young et al.

Chemical Abstracts, vol. 106, no. 21, 25th May 1987, p. 525, abstract 174040k, Columbus, Ohio, US; M. Sawada et al.

Chemical Abstracts, vol. 107, no. 9, 31st August 1987, p. 513, abstract 75549x, Columbus, Ohio, US; S.A. Jones et al.

Angewandte Chemie, International Edition in English, vol. 11, no. 12, 1972, pp. 1061-1072; H. Rembold et al.

(73) Proprietor: **BIORESEARCH S.p.A.**
Via Fosse Ardeatine, 2
I-20060 Liscate (Milano)(IT)

(72) Inventor: **Gennari, Federico**
Via Leonardo da Vinci
Truccazzano (MI)(IT)

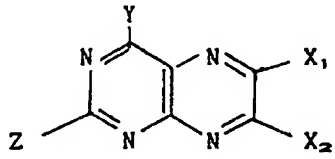
(74) Representative: **Gervasi, Gemma, Dr. et al**
Studio Brevetti e Marchi
NOTARBARTOLO & GERVASI S.r.l.
33, Viale Bianca Maria
I-20122 Milano (IT)

EP 0 290 819 B1

Description

This invention relates to use of pteridines for the preparation of composition with antiamnesic activity.

More particularly, the invention relates to the use of pteridines of the following general formula:



(I)

in which Y and Z, which can be identical or different, are hydrogen, OH or NH_2, and X_1 and X_2, which can be identical or different, are hydrogen, OH, C_1-C_4 alkyl, phenyl, hydroxymethyl or carboxy, for the preparation of compositions with antiamnesic activity.

The pteridines are a class of substances present in numerous living species ranging from the invertebrates and birds to higher mammals including man. They can also be prepared synthetically.

Their biological significance and their participation in many enzymatic reactions have not yet been completely clarified, even though they have been the subject of numerous studies [H. Rembold and W.L. Gyure, Angew. Chem. Internat. Edit. vol II (1972), No. 12, pp 1061, 1072].

We have now surprisingly found that natural or synthetic pteridines of general formula (I) demonstrate activity of positive nootropic type in a test traditionally used in selecting molecules of antiamnesic activity, namely the test of activity towards amnesia induced by electroshock treatment.

Said test, as described by Butler et al. (J. Medicinal Chem. 27, 684, 1984), enables the activity of products able to antagonise retrograde amnesia induced by electroconvulsive shock in the mouse to the evaluated.

It consists of the following operations:

a) conditioning the animal to avoid entering, in a single attempt, a dark chamber in which it would receive an electric shock its paws (passive avoidance);

b) induce retrograde amnesia by electroshock treatment;

c) administer the products under examination to the animal;

d) evaluate the persistance or non-persistance of the conditioning as an index of the absence or, respectively, presence of the amnesia.

The percentage of animals showing retention of the condition after introduction of the amnesia is an index of the antiamnesic activity of the product under examination.

Table 1 shows the results of the use of pteridines of formula (I) in the aforesaid test, showing the percentages of inversion of the amnesia at various doses compared with the control group not subjected to electroshock treatment.

The dose-effect curve is bell-shaped, ie increasing the dose first causes an increase in the effect and then a decrease therein. This pattern is typical of products which influence the cognitive functions.

The greatest effect was observed in the tests at an orally administered dose of 2.5 mg/kg with the products BR 474 and BR 467. In these tests the amnesic action of the electroshock treatment is practically nullified, as demonstrated by the fact that the percentages of animals retaining the conditioning are entirely similar to the control group percentages not subjected to electroshock treatment.

The products were administered orally 90 minutes before evaluating the retention of the conditioning.

Those animals which did not enter the conditioning chamber within 60 seconds were considered amnesia-free.

TABLE 1

No.	CODE	Pteridines of formula (I)	Y	Z	X_1	X_2	% AMNESIA INVERSION Dose mg/kg/os 1.25	2.5	5
1	BR 482	2-amino-4,6,7-trihydroxy pteridine (leucopterin)	OH	NH_2	OH	OH	31.6	86.3	31.6
2	BR 483	2-amino-4,6-dihydroxy pteridine (xanthopterin)	OH	NH_2	OH	H	9.0	20.6	20.6
3	BR 465	2-amino-4-hydroxy-6-methylpteridine	OH	NH_2	CH_3	H	37.5	65.9	57.9
4	BR 466	2-amino-4-hydroxy-7-methylpteridine	OH	NH_2	H	CH_3	38.1	55.7	42.2
5	BR 476	2-amino-4-hydroxy-6-phenylpteridine	OH	NH_2	C_6H_5	H	24.9	57.9	16.9
6	BR 477	2-amino-4-hydroxy-7-phenylpteridine	OH	NH_2	H	C_6H_5	31.7	72.7	18.1

TABLE 1 (continued)

No.	CODE	Pteridines of formula (I)	Y	Z	X_1	X_2	% AMNESIA INVERSION Dose mg/kg/os 1.25	2.5	5
7	BR 464	2-amino-4-hydroxy-6-hydroxymethylpteridine	OH	NH_2	CH_2OH	H	21.5	31.8	31.8
8	BR 469	2-amino-4-hydroxy-6-carboxymethylpteridine	OH	NH_2	COOH	H	9.0	18.1	0
9	BR 468	2-amino-4-hydroxy-pteridine	OH	NH_2	H	H	54.6	57.2	57.2
10	BR 467	2-amino-4-hydroxy-6,7-dimethylpteridine	OH	NH_2	CH_3	CH_3	50.3	100.0	71.5
11	BR 474	2,4-diamino-6,7-dimethyl pteridine	NH_2	NH_2	CH_3	CH_3	12.4	102.6	71.6
12	BR 470	2-amino-6,7-dimethyl pteridine	H	NH_2	CH_3	CH_3	59.0	59.0	37.4
13	BR 471	2,4-hydroxy-6,7-dimethyl pteridine	OH	OH	CH_3	CH_3	50.8	75.4	63.3
14	BR 472	4-hydroxy-6,7-dimethyl pteridine	OH	H	CH_3	CH_3	25.0	56.8	25.0

The pharmacological results obtained in the test demonstrate the effectiveness of the pteridines according to the invention in reducing experimentally induced amnesia and thus the importance of their use in the treatment of cognitive pathologies characterised by memory and vigilance disturbances which are encountered in old age, in some pathologies such as senile dementia of Alzheimer type, multiinfarctual dementia, metabolic encephalopathies and Korsakoff's syndrome, and as a consequence of the abuse of certain therapies (anxiolytic, neuroleptic).

Said pteridines can be used for preparing both injectable forms and oral formulations such as tablets, pills, delayed release capsules, gastroresistant tablets, sachets, syrups, extemporaneous syrups, delayed release syrups and other forms normally used in pharmaceutics.

The pteridines of formula (I) are known products which can be prepared by various methods, such as the method described by C.B. Storm et al. in J. Org. Chem., 36, 3925 (1971).

Advantageously, pteridines of formula (I) are prepared by the process of the present invention, which is based on condensing suitable amino derivatives of pyrimidine with suitable dicarbonyl compounds, in an aqueous medium in the presence of sodium sulphite, at controlled pH.

Some examples are also given of the preparation of pharmaceutical composition containing said pteridines for antiamnesic use.

EXAMPLE 1

Preparation of tablets

a) A 100 mg tablet contains:	
2-amino-4-hydroxy-6,7-dimethyl pteridine	100 mg
crosslinked carboxymethyl cellulose	50 mg
magnesium stearate	10 mg
microcrystalline cellulose	to make up to 400 mg

b) A 100 mg tablet contains:	
2,4-diamino-6,7-dimethyl pteridine	100 mg
corn starch	80 mg
polyvinylpyrrolidone	20 mg
magnesium stearate	10 mg

c) A 100 mg tablet contains:	
2,4-dihydroxy-6,7-dimethyl pteridine	100 mg
sodium chloride	50 mg
polyvinylpyrrolidone	20 mg
corn starch	to make up to 400 mg

d) A 100 mg tablet contains:	
2-amino-4-hydroxy pteridine	100 mg
crosslinked carboxymethyl cellulose	50 mg
magnesium stearate	10 mg
microcrystalline cellulose	to make up to 400 mg

EXAMPLE 2

Preparation of capsules

a) A 100 mg capsule contains:	
2-amino-4-hydroxy-6,7-dimethyl pteridine	100mg
mannitol	100 mg
lactose	100 mg
magnesium stearate	10 g

b) A 100 mg capsule contains:	
2,4-diamino-4-hydroxy-6,7-dimethyl pteridine	100 mg
mannitol	100 mg
lactose	100 mg
magnesium stearate	10 g

EXAMPLE 3

Preparation of gastroresistant tablets

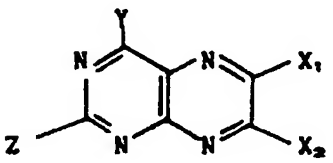
a) A 100 mg tablet contains:	
2-amino-4-hydroxy-6,7-dimethyl pteridine	100 mg
crosslinked carboxymethyl cellulose	70 mg
microcrystalline cellulose	to make up to 400 mg
cellulose acetophthalate	20 mg
diethylphthalate	6.4 mg
silicone resin	3.6 mg

b) A 100 mg tablet contains:	
2,4-diamino-6,7-diethyl pteridine	100 mg
crosslinked polyvinylpyrrolidone	100 mg
sodium chloride	50 mg
microcrystalline cellulose	to make up to 400 mg
cellulose acetophthalate	20 mg
diethylphthalate	20 mg
silicone resin	3.6 mg

c) A 100 mg tablet contains:	
2-amino-6,7-dimethyl pteridine	100 mg
sodium bicarbonate	100 mg
citric acid	50 mg
cellulose acetophthalate	20 mg
diethylphthalate	6.4 mg
silicone resin	3.6 mg

Claims

1. The use of pteridines of general formula (I):



(I)

in which Y and Z, which can be identical or different, are hydrogen, OH or NH_2, and X_1 and X_2, which

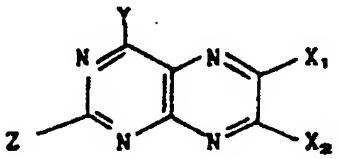
can be identical or different, are hydrogen, OH, C_1-C_4 alkyl, phenyl, hydroxymethyl or carboxyl, for the preparation of pharmaceutical compositions for the treatment of cognitive pathologies characterised by memory and vigilance disturbances, such as senile dementia of Alzheimer type, multiinfarctual dementia, metabolic encephalopathies, Korsakoff's syndrome, and the consequences of the abuse of certain therapies such as anxiolytic and neuroleptic.

2. The use as claimed in claim 2, wherein the pharmaceutical compositions are presented in injectable form.

3. The use as claimed in claim 1, wherein the pharmaceutical compositions are presented in forms suitable for oral use such as tablets, pills, capsules, delayed release capsules, gastroresistant tablets, sachets, syrups, extemporaneous syrups and delayed release syrups.

Patentansprüche

1. Verwendung von Pteridinen der allgemeinen Formel (I)



(I)

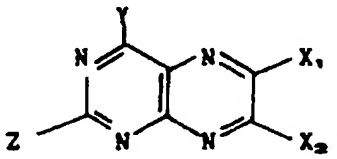
worin Y und Z, die gleich oder verschieden sein können, Wasserstoff, OH oder NH_2 sind, und worin X_1 und X_2 , die gleich oder verschieden sein können, Wasserstoff, OH, C_{1-4}-Alkyl, Phenyl, Hydroxymethyl oder Carboxyl sind, für die Herstellung von pharmazeutischen Zusammenstzungen für die Behandlung von kognitiven Pathologien,
gekennzeichnet durch Gedächtnis- und Schlaflosigkeitsstörungen wie senile Dementia vom Alzheimer Typ, Multiinfarktdementia, metabolische Encephalopathien, Korsakoff's Syndrom und die Folgen des Mißbrauches von gewissen Therapien wie angstlösende und Neuroleptische.

2. Verwendung nach Anspruch 1,
dadurch **gekennzeichnet**, daß die pharmazeutischen Zusammensetzungen in injizierbarer Form vorhanden sind.

3. Verwendung nach Anspruch 1,
dadurch **gekennzeichnet**, daß die pharmazeutischen Zusammensetzungen in Formen vorhanden sind, die für die orale Verwendung geeignet sind, wie Tabletten, Pillen, Kapseln, Kapseln mit verzögerter Freilassung, magenresistente Tabletten, Säckchen, Sirupe, nicht fertige Sirupe und Sirupe mit verzögerter Freilassung.

Revendications

1. L'utilisation de ptéridines de formule générale (I):



(I)

dans laquelle Y et Z, qui peuvent être identiques ou différents, sont l'hydrogène, OH ou NH_2, et X_1 et X_2, qui peuvent être identiques ou différents, sont l'hydrogène, OH, un groupe alkyle en C_1-C_4,

phényle, hydroxyméthyle ou carboxyle, pour la préparation de compositions pharmaceutiques pour le traitement de pathologies cognitives caractérisées par des défauts de mémoire et de vigilance, telles que la démence sénile du type Alzheimer, la démence multi-infarctuelle, les encéphalopathies métaboliques, le syndrome de Korsakoff, et les conséquences de l'abus de certaines thérapies telles que les anxiolytiques et les neuroleptiques.

2. L'utilisation selon la revendication 1, dans laquelle les compositions pharmaceutiques sont présentées sous forme injectable.

3. L'utilisation selon la revendication 1, dans laquelle les compositions pharmaceutiques sont présentées sous forme adaptée à l'utilisation orale, telle que comprimés, pilules, gélules, gélules à libération retardée, comprimés gastrorésistants, sachets, sirops, sirops extemporanés et sirops à libération retardée.